Synthetic Applications of Imidotitanium–Alkyne [2 + 2] Cycloadditions. A Concise, Stereocontrolled Total Synthesis of the Antifungal Agent (+)-Preussin†

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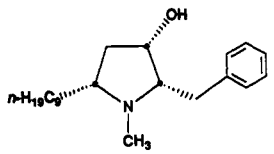
Abstract: An efficient stereoselective total synthesis of (+)-preussin, (2*S*,3*S*,5*R*)-1-methyl-5-nonyl-2-(phenylmethyl)-3-pyrrolidinol (**1**), was achieved by way of a convergent, intramolecular imidotitanium–alkyne [2 + 2] cycloaddition–acyl cyanide condensation sequence.

Introduction. The potent antifungal agent (+)-preussin (L-657,398) (**1**) is a structurally novel pyrrolidine alkaloid which was recently isolated from fermentation broths of *Aspergillus ochraceus* ATCC 22947.[2] Both **1** and its acylated derivatives possess significant activity as broad-spectrum antibiotics against yeasts and filamentous fungi. In this connection, it is noteworthy that **1** exhibits a considerably greater range of activity than the antibiotic anisomycin (**2**).[2] There is at present only one reported synthesis for this deceptively simple molecule.[3] We envisioned that a highly convergent and stereocontrolled total synthesis of (+)-preussin (**1**) could be achieved by way of an intramolecular Group IV metal-mediated alkyne amination.



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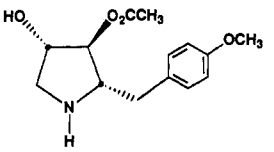

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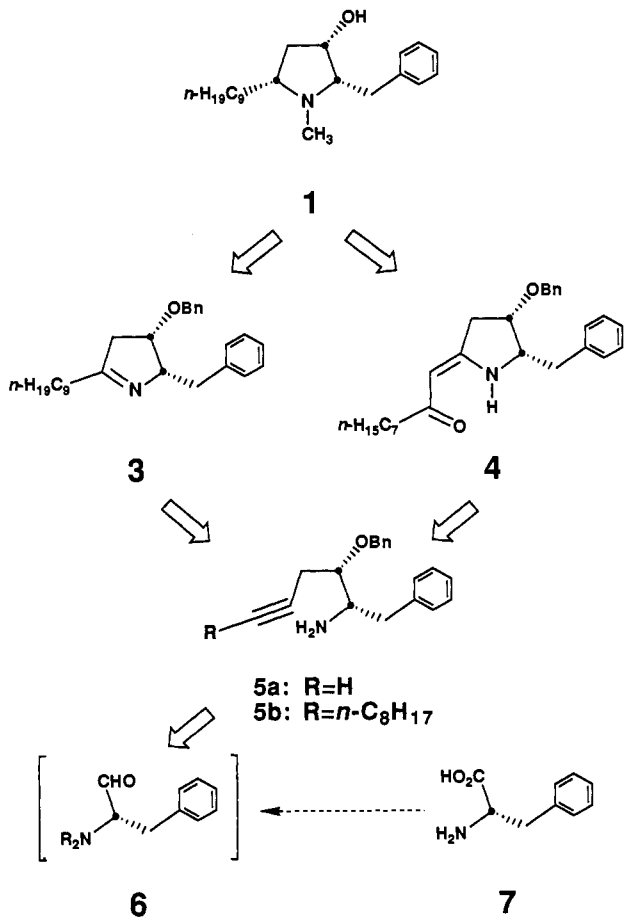
In 1992, we reported the first examples of intramolecular imidotitanium–alkyne [2 + 2] cycloadditions as well as the utilization of this methodology for the synthesis of tetrahydropyridines and functionalized dihydropyrrole derivatives.[4] The preparative utility of a catalytic variation of this cycloaddition was subsequently demonstrated in an efficient total synthesis of the indolizidine alkaloid (±)-monomorine.[5] The present work describes the successful application of an imidotitanium–alkyne [2 + 2] cycloaddition to the total synthesis of (+)-preussin (**1**). In addition, the synthetic route described here should be readily extendable to the preparation of structural analogs possessing varied 2-arylmethyl and 5-alkyl substituents as well as other possible combinations of absolute stereochemistry. At the outset of these studies, our synthetic approach was guided by the divergent–convergent strategy illustrated in Scheme I.

Accordingly, it was envisaged that (+)-preussin (**1**) would be preparable via *stereoselective* reductive methylation of Δ^1-pyrroline **3** or by the appropriate manipulation of the vinylogous amide **4**. The cyclic intermediates **3** and **4** were projected to retrosynthetically converge on the interrelatable alkynyl amines **5a** and **5b**. To this end, intramolecular alkyne aminolysis of **5b** catalyzed by $CpTiCl_3$[4,5] was expected to provide **3**. Alternatively, exposure of **5a** to a stoichiometric amount of $CpTi(CH_3)_2Cl$ (**17a**) followed by interception of the resultant azatitanetine by octanoyl cyanide (**19**)[4] was seen, in principle, as a source of **4**. The availability of the alkynyl amine **5a** was predicated on a chelation-controlled addition[7a–c] of allenylmagnesium bromide[8] to an appropriate homochiral aldehyde, **6**, derived from L-(−)-phenylalanine (**7**).[9] In addition to the highly flexible nature of the synthetic plan outlined above, the subjection of the torsionally

Scheme I



† This paper is dedicated to the memory of Professor Paul G. Gassman.
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(1) Fellow of the Alexander von Humboldt Foundation 1993–94.
(2) (a) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A. *J. Antibiot.* **1988**, *41*, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184.
(3) Pak, C. S.; Lee, G. H. *J. Org. Chem.* **1991**, *56*, 1128.
(4) McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459.
(5) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323.

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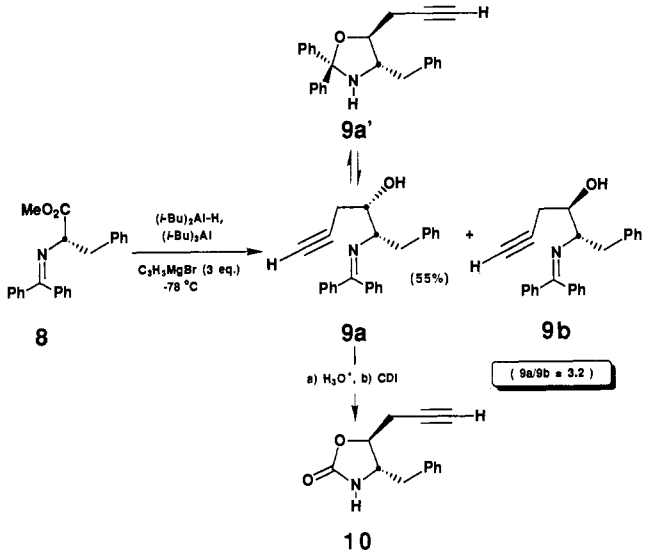
biased alkynyl amines **5a** and **5b** to internal cycloaddition via the corresponding imidotitanium complexes was expected to more fully clarify the scope of this new annulation reaction. The results of these studies as well as the successful application of an imidotitanium–alkyne [2 + 2] cycloaddition to the total synthesis of (+)-preussin (**1**) are detailed below.

Synthesis of Alkynyl Amine 5b and Cyclization Studies. Relatively few methods have been reported for the preparation and subsequent utilization of homochiral α-amino aldehyde equivalents.[10,11] Of these, the procedure recently described by Polt[11] appeared ideally suited for the synthesis of precursors to the alkynyl amine **5a**. Polt has reported that the direct reduction/arylation of *N*-diphenylmethylene derivatives (O'Donnell's Schiff bases)[12] of amino esters provides the corresponding *threo* 2° alcohol derivatives selectively (*threo*/*erythro* ≃ 8:1) in good yield.[11] We were somewhat disappointed but not surprised at the discovery that the corresponding reduction/*propargylation* sequence proceeds with reduced stereoselectivity. Accordingly, exposure of methyl *N*-(diphenylmethylene)-L-phenylalaninate (**8**)[11] to a 1:1 mixture of *i*-Bu_2AlH and *i*-Bu_3Al (1 equiv each) in the presence of allenylmagnesium bromide[8] [3 equiv, −73 °C (10 h) → 15 °C (4 h)] provided a 3.2:1 mixture of the *threo* and *erythro* homopropargyl alcohols **9a** and **9b** in 95% yield (unpurified). The desired *threo* isomer **9a** was readily isolated from this mixture (55% yield from **8**) by column chromatography on silica gel. In consonance with the observations of Polt[11] on structurally related *threo* imino alcohols, the major adduct formed in this reaction was found to exist as an equilibrium mixture of the acyclic imine isomer **9a** and the cyclic oxazolidine isomer **9a'** at room temperature. Support for the stereochemical assignment of **9a** was obtained by chemical derivatization. To this end, sequential hydrolytic cleavage of the diphenylmethylene moiety ($H_2C_2O_4$–H_2O) followed by treatment of the resultant amino alcohol with carbonyldiimidazole furnished the crystalline oxazolidinone **10**. The vicinal coupling constant of 6.6 Hz for the OCH–HCN resonances of **10** was consistent with that reported for a closely related oxazolidinone.[11] Conclusive proof of the absolute stereochemistry of **9a** was ultimately obtained by its conversion into (+)-preussin (**1**). The elaboration of the precyclization intermediate **5b** from **9a** was readily accomplished in 52% overall yield by sequential O-benzylation (KH–THF, $PhCH_2Br$) followed by acetylide alkylation [(a) LDA and (b) *n*-$C_8H_{17}I$] and a final imine hydrolysis ($H_2C_2O_4$–H_2O).

Having secured the putative "key precyclization substrate" **5b**



by way of the efficient procedure outlined above, we set out to effect its cyclization through the use of the imidotitanium–alkyne [2 + 2] cycloaddition described previously.[4,5] To our dismay, **5b** proved resistant to cyclization under the standard sets of reaction conditions (either catalytic or stoichiometric in Ti) reported earlier.[4] In addition, imidozirconium complexes[4] derived from **5b** also failed to undergo internal cycloaddition at 25 °C. The foregoing reactions led to the recovery of **5b** after a hydrolytic quench in consonance with the preferential formation of metal imido dimers.[6] Presumably, unfavorable torsional features intrinsic to the imido complexes derived from **5b** are responsible for the observed lack of cyclization *under ambient conditions*. In addition, the thermal lability of the complexes $CpTi(CH_3)_2Cl$ (**17a**) and $CpZr(CH_3)_2Cl$ (**17b**) precluded the use of "high-dilution" techniques involving the slow, inverse addition of **5b** *to* these reagents at elevated temperatures. In an effort to prepare a more thermally stable *titanium* catalyst, $CpTiCl_3$ was treated with 2 equiv of $LiNEt_2$ *in situ* to generate the bis(ethylamido) species $CpTiCl(NEt_2)_2$ (**11**). This new complex has proven an *unusually* reactive catalyst for effecting imidotitanium–alkyne [2 + 2] cycloadditions at elevated temperatures.[13] It was readily established that the cyclization of **5b** *could* be achieved in the presence of $CpTiCl(NEt_2)_2$ (**11**). Unfortunately, the conditions required for cyclization were sufficiently vigorous (1,2-DME, 83 °C) to cause the initially formed Δ¹-pyrroline **3** to undergo sequential tautomerization–elimination, leading to pyrrole **12** in 53% unoptimized yield (Scheme II).

Synthesis and Cyclization of Amine 5a to Azatitanetine 18, a Total Synthesis of (+)-Preussin (1). As part of a parallel investigation, it was discovered that primary amines bearing *terminal alkyne moieties* (e.g., **13**) undergo *exceptionally facile stoichiometric or catalytic* imidotitanium–alkyne [2 + 2] cycloadditions.[13]

In light of these results, it was predicted that amine **5a** would undergo cyclization under reaction conditions that were far less strenuous than those required for **5b**. To examine this possibility, amine **5a** was trivially prepared in 75% isolated yield by O-benzylation of **9a** (KH–THF, $PhCH_2Br$) followed by hydrolysis ($H_2C_2O_4$–H_2O) of the resultant imino ether **16**.

In agreement with our expectation, exposure of **5a** to $CpTi(CH_3)_2Cl$ (**17**) in THF *at 25 °C* gave rise to the efficient generation of the reactive azatitanetine **18**. In contrast to our earlier findings, the condensation of **18** *in situ* with octanoyl cyanide (**19**) (1.1 equiv) *did not* lead to the formation of the anticipated vinylogous

(6) For additional recent references relating to Group IV metal–imido complexes, see: (a) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 8729. (b) Carney, M. J.; Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8751. (c) Cummins, C. C.; Baxter, S. M.; Wolczanski, P. T. *J. Am. Chem. Soc.* **1988**, *110*, 8731. (d) Hill, J. E.; Profilet, R. D.; Fanwick, P. E.; Rothwell, I. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 664. (e) Roesky, H. W.; Voelker, H.; Witt, M.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 669. (f) Cummins, C. C.; Schaller, C. P.; VanDuyne, G. D.; Wolczanski, P. T.; Chan, A. W. E.; Hoffmann, R. *J. Am. Chem. Soc.* **1991**, *113*, 2985. (g) Doxsee, K. D.; Farahi, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7239. (h) Doxsee, K. D.; Farahi, J. B.; Hope, H. *J. Am. Chem. Soc.* **1991**, *113*, 8889.

(7) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. Selected previous examples of this type of chelation-controlled addition include the following. (b) Duhamel, P.; Duhamel, L.; Gralak, J. *Tetrahedron Lett.* **1972**, *13*, 2329. (c) Sicher, J.; Svoboda, M.; Hrdá, M.; Rudinger, J.; Šorm, F. *Coll. Czech. Chem. Commun.* **1953**, 487.

(8) Brandsma, L. *Preparative Acetylene Chemistry*, 2nd ed.; Elsevier Science Publishers: Amsterdam, The Netherlands, 1988.

(9) For previous synthesis of homochiral pyrrolidines from amino acids, see: (a) Rapoport, H.; Shiosaki, K. *J. Org. Chem.* **1985**, *50*, 1229. (b) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539. (c) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.

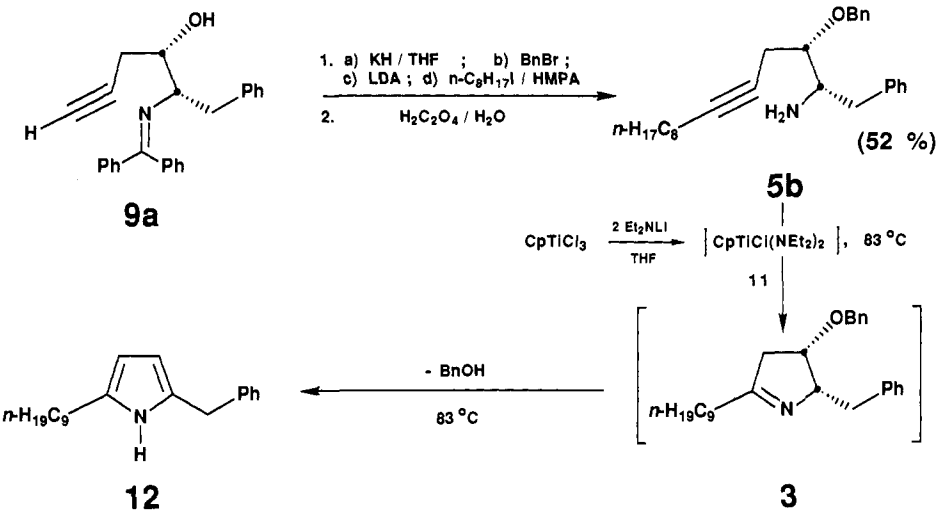
(10) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(11) Polt, R.; Peterson, M. A.; DeYong, L. *J. Org. Chem.* **1992**, *57*, 5469. In addition, these authors have shown that the corresponding direct reduction/*vinylation* sequence proceeds with excellent diastereoselectivity. The authors thank Professor Polt for kindly providing a copy of this manuscript prior to publication.

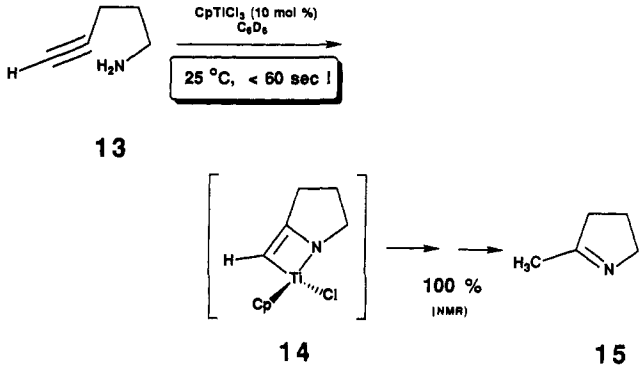
(12) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

(13) McGrane, P. L. Ph.D. Dissertation, Montana State University, January 1993. In this connection, it is noteworthy that the *non-cyclopentadienyl*-bearing Lewis acid $TiCl_4$ is *ineffective* as a cyclization catalyst for representative alkynyl amines.

Scheme II



amide **4**. Instead, the α,β-unsaturated nitrile **20** was formed with good overall efficiency (76% yield, 60% chromatographed yield).[14] The product directly obtained in the above manner was



sufficiently pure to be carried on through the next series of reactions without rigorous purification.[15] N-Methylation of **20** ($CH_3O_3SCF_3$–CH_2Cl_2, 25 °C) followed by direct reduction of the resulting iminium salt *in situ* ($NaBH_3CN$–CH_3OH, 25 °C) provided pyrrolidine **21** as a single stereoisomer in 81% isolated yield. Reduction of the carbon–carbon double bond within **21** was achieved in 90% yield by exposure to Mg^0 in CH_3OH[16] to secure pyrrolidines **22** as a mixture of diastereomers at the nitrile-bearing carbon. Purification at this stage could easily be accomplished by column chromatography on silica gel to reproducibly provide the diastereomeric pyrrolidines **22** in 35–44% *overall yield* from amine **5a**.[15] The reductive cleavage of the cyano moiety from pyrrolidines **22** proved problematic under conventional reaction conditions[17] owing to the competing reduction of the phenylmethyl substituent. However, the efficient deletion of the cyano group could be effected via the agency of potassium metal in HMPA–diethyl ether containing a sacrificial quantity of toluene. Under this set of conditions, reductive O-debenzylation was also achieved. In accord with literature precedent, reductive decyanation was also accompanied, to a small extent, by the formation of olefinic products resulting from the formal elimination of the cyanide ion. Accordingly, direct hydrogenation of the crude material obtained from the foregoing reaction (H_2/Pd–C) provided chemically pure (+)-preussin (**1**) in 85% isolated yield from diastereomeric **22**. The spectroscopic and physical properties of the material obtained in the above manner were in excellent agreement with those reported for natural[2] and synthetic[3] (+)-preussin (**1**) (Scheme III).

The enantio-defined total synthesis of (+)-preussin (**1**) described above is prominently characterized by its efficiency and highly convergent nature. Additional applications of Group IV metal-mediated alkyne aminations to problems of synthetic interest will be reported in future accounts from these laboratories.

Experimental Section[19]

Methyl *N*-(Diphenylmethylene)-L-phenylalaninate (8). The preparation of this compound has been described by Polt.[11] **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–6.60 (m, 15H, Ph), 4.29 (dd, J = 9.3 and 4.3 Hz, 1H, NC*H*), 3.74 (s, 3H, C*H*$_3$), 3.31 (dd, J = 13.3 and 4.3 Hz, 1H, PhC*H*), 3.21 (dd, J = 13.3 and 9.3 Hz, 1H, PhC*H*); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 172.17, 170.74, 139.29, 137.82, 135.97, 130.17, 129.76, 128.68, 128.24, 128.06, 127.90, 127.53, 126.22, 67.13, 52.06, 39.70.

(2*S*,3*S*)- and (2*S*,3*R*)-2-[*N*-(Diphenylmethylene)amino]-1-phenylhex-5-yn-3-ol (9a and 9b). A 1-L flask charged with methyl *N*-(diphenylmethylene)-L-phenylalaninate (**8**) (19.5 g, 57 mmol) and CH_2Cl_2 (440 mL) was cooled to –73 °C. A mixture of TriBAL (1 M in C_7H_8, 57 mL, 1 equiv) and DiBAL-H (1 M in C_7H_8, 57 mL, 1 equiv) was then added slowly via an addition funnel so that the temperature did not exceed –68 °C. Upon completion of the addition, the yellow solution was treated with $H_2C{=}C{=}C(H)MgBr$ (1.8 M in Et_2O, 95 mL, 3 equiv), again at a rate such that the temperature did not exceed –68 °C. The resulting green reaction mixture was stirred for 10 h at –73 °C before it was allowed to slowly warm to 15 °C over 4 h. After the solution was cooled to 0 °C, aqueous NaOH (5 M, 63 mL) was slowly added over 1 h. The red organic layer was then decanted, and the aqueous layer was extracted with 3 × 100 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, and the solvents were evaporated. The residue was rediluted with CCl_4 and filtered through a pad of basic alumina. Concentration *in vacuo* gave 19.15 g (55.8 mmol, 95%) of the diastereomeric mixture of **9a** and **9b** as a viscous red oil. When 10 g of this mixture was chromatographed on 600 mL of silica gel (10% EtOAc/hexane for elution), there were obtained 5.755 g (16.8 mmol, 55%) of the 2*S*,3*S* diastereomer **9a** as a yellow-green, gelatinous solid and 1.761 g (4.99 mmol, 16.8%) of the 2*S*,3*R* diastereomer **9a** as a white solid.

(2*S*,3*S*)-2-[*N*-Diphenylmethylene)amino]-1-phenylhex-5-yn-3-ol (9a) (note, oxazolidine–hydroxyimine isomerization): $[\alpha]^{25}_D$ +2.5° (*c* 10.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–6.70 (m, 15H, Ph), 3.93 (app q, J = 6.7 and 6.0 Hz, 0.6H, NC*H*), 3.83 (app t, J = 6.4 Hz, 0.4H), 3.75 (app dt, J = 7.0, 6.2, and 1.7 Hz, 0.4H), 3.47 (app q, J = 7.4 and 5.7 Hz, 0.6H), 3.06, 2.95, 2.88, and 2.86 (all dd, J = 13.2 and 6.8 Hz,

(14) Studies are currently underway to determine whether this unexpected mode of condensation is general for azatitanetines derived from *terminal* alkynes.

(15) All new compounds were fully characterized by IR, MS, and ^{1}H and ^{13}C NMR and possessed satisfactory combustion analyses or exact mass.

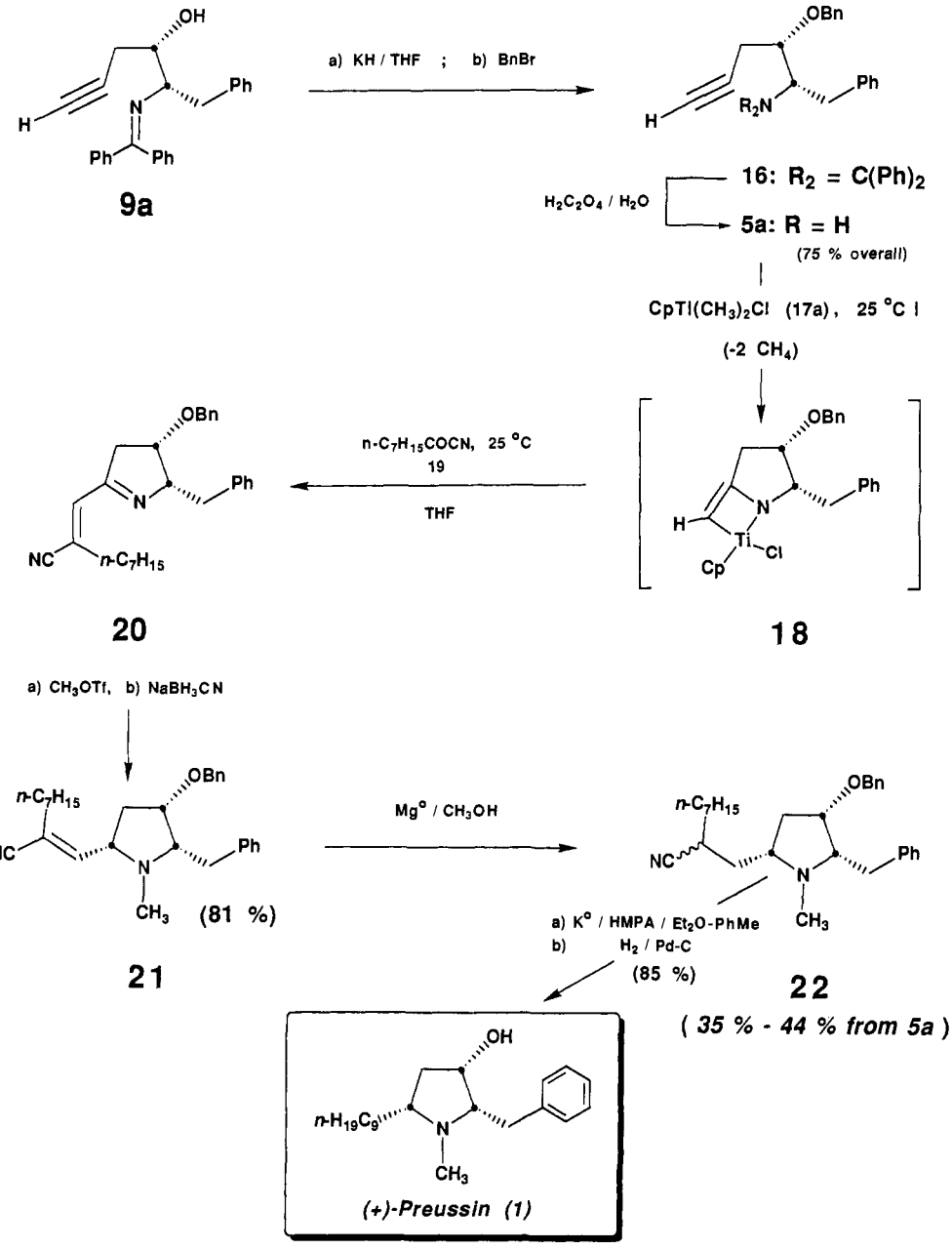
(16) Profitt, J. A.; Watt, D. S. *J. Org. Chem.* **1975**, *40*, 127.

(17) Cuvigny, T.; Larcheveque, M.; Normant, H. *Bull. Soc. Chim. France* **1973**, 1174.

(18) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 4089.

(19) General experimental details may be found in ref 18.

Scheme III



14.1 and 5.7 Hz, 13.2 and 4.5 Hz, and 14.1 and 8.0 Hz, respectively, 2H, PhCH_2), 2.46 and 2.40 (m, 1H, C≡CCH), 2.32–2.18 (m, 1H, C≡CCH), 1.97 (app, t, J = 2.7 and 2.4 Hz, 0.6H, C≡CH), 1.92 (app t, J = 2.7 and 2.4 Hz, 0.4H, C≡CH); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 169.92, 144.94, 144.78, 139.10, 138.42, 138.32, 136.09, 130.33, 129.77, 129.02, 128.41, 128.19, 128.10, 128.04, 127.98, 127.62, 127.49, 127.28, 126.40, 126.19, 126.09, 126.05, 99.45, 80.89, 80.62, 79.91, 71.00, 70.14, 65.50, 64.77, 39.54, 39.37, 25.52, 24.00; IR (film) 3460, 3250, 3050, 3030, 2990, 2890, 2100, 1655, 1615, 1595, 1485, 1445, 1310, 1275, 1240, 1065, 1030, 950, 780, 755, 710 cm^{-1}; high-resolution mass spectrum calcd for $C_{25}H_{23}NO$ (M^+) 353.1781, found 353.1780.

(2*S*,3*R*)-2-[*N*-(Diphenylmethylene)amino]-1-phenylhex-5-yn-3-ol (9b): $[\alpha]^{25}_D$ –80.7° (*c* 10.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–6.30 (m, 15H, Ph), 3.94 (app q, J = 5.4 Hz, 1H, OCH), 3.64 (ddd, J = 9.5, 5.4, and 3.1 Hz, 1H, NCH), 3.05 (dd, J = 13.0 and 3.1 Hz, 1H, PhCH), 2.90 (dd, J = 13.0 and 9.5 Hz, 1H, PhCH), 2.68 (br s, 1H, OH), 2.57 (ddd, J = 16.7, 5.6, and 2.7 Hz, 1H, C≡CCH), 2.48 (ddd, J = 16.7, 7.5, and 2.5 Hz, 1H, C≡CCH), 1.98 (app t, J = 2.7 and 2.5 Hz, 1H, C≡CH); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 168.79, 139.56, 138.94, 136.30, 130.18, 130.00, 128.46, 128.11, 127.97, 127.85, 127.65, 125.94, 80.88, 73.01, 70.75, 67.03, 37.83, 23.73; IR (KBr) 3230, 3090, 3010, 2990, 2905, 2850, 2100, 1605, 1480, 1440, 1325, 1280, 1105, 1045, 1015, 775, 690 cm^{-1}; high-resolution mass spectrum calcd for $C_{25}H_{23}NO$ (M^+) 353.1781, found 353.1779.

(2*S*,3*S*)-3-(Benzyloxy)-2-[*N*-(diphenylmethylene)amino]-1-phenylhex-5-yne (16). A solution of **9a** (5.4 g, 15.3 mmol) in THF (30 mL) was added over 15 min to a suspension of KH (1.2 g, 30 mmol) in THF (50 mL) at 25 °C. After 2 h at 25 °C, the dark red solution was cooled to 0 °C and $PhCH_2Br$ (3.57 mL, 30 mmol) was added. After 10 min at 0 °C, the mixture was warmed to 25 °C for 1 h. The reaction mixture was then poured into ice water (100 mL) and Et_2O (100 mL). The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. After redrying as a solution in 1:1 CH_2Cl_2–pentane, the solvents were again evaporated *in vacuo* to yield 6.916 g (102%) of crude **16**. An analytical sample was prepared by chromatography on silica gel (5% EtOAc/hexane for elution): $[\alpha]^{25}_D$ –64.2° (*c* 10.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–6.40 (m, 20 H, Ph), 4.76 (d, J = 11.8 Hz, 1H, PhCHO), 4.62 (d, J = 11.8 Hz, 1H, PhCHO), 3.89 (ddd, J = 9.8, 5.35, and 3.0 Hz, 1H, NCH), 3.75 (ddd, J = 7.6, 5.35, and 3.7 Hz, 1H, OCH), 3.09 (dd, J = 12.8 and 3.0 Hz, 1H, PhCH), 2.96 and 2.94 (overlapping dd, J = 12.8 and 9.8 Hz, 1H, PhCH and ddd, J = 17, 3.7, and 2.4 Hz, 1H, C≡CCH), 2.69 (ddd, J = 17. 7.6, and 2.7 Hz, 1H, C≡CCH), 1.34 (app t, J = 2.7 and 2.4 Hz, 1H, C≡CH); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 168.52, 139.67, 139.30, 138.49, 136.50,

129.80, 129.73, 128.36, 128.12, 127.97, 127.88, 127.82, 127.75, 127.65, 127.58, 127.37, 125.74, 82.14, 80.47, 72.51, 69.53, 66.36, 37.31, 20.94; IR (film) 3270, 3050, 3000, 2900, 2115, 1740, 1650, 1625, 1490, 1455, 1445, 1910, 1275, 1240, 1060, 1025, 745, 695 cm^{-1}; high-resolution mass spectrum calcd for $C_{32}H_{28}NO$ ($M - H^+$) 442.2211, found 442.2216.

[(2*S*,3*S*)-3-(Benzyloxy)-1-phenylhex-5-yn-2-yl]amine (5a). A solution of **16** (7.24 g, 16.35 mmol) and oxalic acid monohydrate (2.6 g, 20 mmol) in THF (30 mL), H_2O (1 mL), and CH_3OH (6 mL) was allowed to stir for 3 h at 25 °C. A solution of KOH (1.2 g) in H_2O (25 mL) was then added. The mixture was transferred to a separatory funnel and extracted with hexane (1 × 20 mL) and 1:1 Et_2O–hexane (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography of the crude product on silica gel (10% EtOAc/hexane–5% CH_3OH/CH_2Cl_2 for elution) afforded 3.42 g (75%) of **5a** as a viscous light yellow oil: $[\alpha]^{25}_D$ +23.3° (*c* 10.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.10 (m, 10H, Ph), 4.74 (d, *J* = 11.5 Hz, 1H, PhC*H*O), 4.51 (d, *J* = 11.5 Hz, 1H, PhC*H*O), 3.48 (m, 1H, OC*H*), 3.24 (app pent, *J* = 4.6 Hz, 1H, NC*H*), 2.87 (dd, *J* = 13.3 and 5.0 Hz, 1H, PhC*H*), 2.70–2.50 (m, 3H, C≡CC*H* and PhC*H*), 2.01 (app t, *J* = 2.7 Hz, 1H, C≡C*H*), 1.41 (s, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 139.29, 138.25, 129.20, 128.47, 128.40, 127.84, 127.73, 126.24, 81.12, 79.92, 72.31, 70.23, 55.09, 41.18, 20.76; IR (film) 3290, 3010, 2900, 2110, 1590, 1490, 1450, 1340, 1060, 1020, 770, 690 cm^{-1}; high-resolution mass spectrum calcd for $C_{19}H_{22}NO$ (MH^+) 280.1702, found 280.1703. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.63; H, 7.51.

Octanoyl Cyanide (19). Octanoyl chloride (4.27 mL, 25 mmol) was added to a suspension of CuCN (2.69 g, 30 mmol) in CH_3CN (30 mL). The resultant mixture was brought to reflux for 30 min, at which time the CH_3CN was allowed to distill from the reaction mixture. The crude product was then distilled from the copper salts under aspirator pressure. Redistillation at aspirator pressure (98–102 °C) afforded 2.5 g (65%) of **19** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (t, *J* = 7.3 Hz, 2H, CH_2CO), 1.71 (app pent, *J* = 7.3 Hz, 2H, CH_2CH$_2$CO), 1.40–1.20 (complex m, 8H, 4CH_2), 0.87 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 177.06, 113.24, 44.98, 31.38, 28.68, 28.48, 22.72, 22.43, 13.89; IR (film) 2910, 2845, 2205, 1725, 1460, 1380, 1370, 1120, 1070, 1015, 740 cm^{-1}.

(4*S*,5*S*)-4-(Benzyloxy)-2-(2′-cyano-1′-nonen-1′-yl)-5-(phenylmethyl)-2*H*-pyrrole (20). A solution of $CpTiCl_3$ (230 mg, 1.05 mmol) in THF (3 mL) at 25 °C was treated with CH_3Li (1.8 M in Et_2O, 1.17 mL, 2.10 mmol). After 15 min, the mixture was cooled to 0 °C and **5a** (270 mg, 0.97 mmol) in THF (1 mL) was added. The mixture was then stirred for 2 h in the dark at 25 °C. The dark burgundy solution was then cooled to 0 °C, and **19** (168 mg, 1.1 mmol) was added. After 2 h at 25 °C, Florisil (~0.5 g) and hexane (5 mL) were added. The resultant slurry was filtered through Florisil (2 in.) with the aid of 1:1 Et_2O–hexane (50 mL) for elution. Concentration of the organic phases provided crude **20** (307 mg, 76%) as a yellow oil. The analytically pure product was isolated by column chromatography on silica gel (10% EtOAc/hexane for elution) in 60% yield. *However, better overall yields were obtained when crude **20** was employed in the preparation of **21***: ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.15 (m, 10H, Ph), 6.92 (s, 1H, C=C*H*), 4.56 (d, *J* = 11.7 Hz, 1H, PhC*H*O), 4.33 (d, *J* = 11.7 Hz, 1H, PhC*H*O), 4.25–4.12 (m, 2H, NC*H* and OC*H*), 3.41 (d, *J* = 17.7 Hz, 1H, PhC*H*), 3.33 (dd, *J* = 13.8 and 6.5 Hz, 1H, N=CC*H*), 3.23 (dd, *J* = 13.8 and 8.2 Hz, 1H, N=CC*H*), 2.97 (ddd, *J* = 17.7, 5.0, and 1.3 Hz, 1H, PhC*H*), 2.39 (t, *J* = 7.46 Hz, 2H, C=CCH_2), 1.64 (m, 2H, CH_2), 1.45–1.25 (complex m, 10H, 5CH_2), 0.93 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 168.63, 139.83, 139.80, 137.74, 129.02, 128.20, 128.13, 127.45, 125.86, 120.29, 117.51, 78.20, 76.81, 71.20 41.82, 35.98, 34.84, 31.43, 28.68, 28.43, 27.66, 22.40, 13.85; IR (film) 3020, 3000, 2930, 2900, 2850, 2195, 1700, 1495, 1455, 1345, 1100, 1060, 1030, 730, 690 cm^{-1}; MS (ESI^+) chemical mass calcd for $C_{28}H_{35}N_2O$ (MH^+) 415.6, found 415.6. Anal. Calcd for $C_{28}H_{34}N_2O$: C, 81.12; H, 8.27. Found: C, 80.80; H, 8.54.

(2*S*,3*S*,5*R*)-4-(Benzyloxy)-2-(2′-cyano-1′-nonen-1′-yl)-1-methyl-5-(phenylmethyl)pyrrolidine (21). To a solution of crude **20** (307 mg, 0.741 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added $CH_3O_3SCF_3$ (100 μL, 0.888 mmol). After 2 h at 25 °C, the reaction mixture was cooled to −72 °C and a solution of $NaBH_3CN$ (56 mg, 0.888 mmol) in CH_3OH (1 mL) was added via syringe. The cooling bath was removed, and the mixture was then stirred vigorously for 2 h at 25 °C. After the reaction was quenched with 1 M NaOH (3 mL), the mixture was diluted with pentane (4 mL). The organic phase was separated and combined with two 1:1 CH_2Cl_2–pentane extractions (3 mL) of the aqueous phase. The organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford **21** (258 mg, 81%) as an orange oil. An analytical sample was prepared by column chromatography on silica gel (5% EtOAc/hexane for elution): ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.10 (m, 10H, Ph), 6.17 (d, *J* = 9.3 Hz, 1H, C=C*H*), 4.43 (d, *J* = 11.6 Hz, 1H, PhC*H*O), 4.22 (d, *J* = 11.6 Hz, 1H, PhC*H*O), 3.72 (m, *J* = 2.3 Hz, 1H, OC*H*), 3.25 (app q, *J* = 8.6 Hz, 1H, NC*H*C=C), 3.04 (dd, *J* = 13.2 and 10.1 Hz, 1H, PhC*H*), 2.83 (dd, *J* = 13.2 and 4.3 Hz, 1H, PhC*H*), 2.56 (app p, *J* = 5.0 and 4.5 Hz, 1H, NC*H*Bn), 2.31 (s, 3H, NCH_3), 2.28–2.17 (m, 3H, C=CCH_2 and β-*H*), 1.64 (ddd, *J* = 13.9, 7.4, and 2.3 Hz, 1H, α-*H*), 1.53 (m, 2H, CH_2), 1.26 (m, 8H, 4CH_2), 0.87 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 149.32, 139.69, 139.25, 129.26, 128.23, 128.17, 127.97, 127.52, 125.89, 117.37, 115.94, 77.55, 72.64, 71.02, 66.00, 39.30, 36.45, 34.16, 33.87, 31.62, 28.81, 28.52, 27.84, 22.52, 13.95; IR (film) 3050, 3000, 2900, 2850, 2190, 1470, 1440, 1330, 1140, 1085, 1055, 1020, 755, 690 cm^{-1}; high-resolution mass spectrum calcd for $C_{29}H_{38}N_2O$ (M^+) 430.2985, found 430.2988.

Diastereomeric Nitriles 22. To unpurified **21** (250 mg, 0.58 mmol) in absolute CH_3OH (5 mL) were added magnesium turnings (0.56 g, 23 mmol). The flask was then placed in a water bath at 25 °C and stirred for 5 h. The mixture was concentrated *in vacuo* and then subjected to high vacuum. The resultant amorphous mass was triturated with hexane (3 × 4 mL). After the supernatant solution was filtered through a plug of Florisil, the organic phases were concentrated *in vacuo* to afford **22** (230 mg, 90%) as a reddish oil. Chromatographic purification on silica gel (5% EtOAc/hexane for elution) provided 147–185 mg (*35–44% from **5a***) of the diastereomeric mixture **22**. The ^1H NMR spectrum of the mixture (supplementary material) exhibits two NCH_3 resonances in a ratio of 0.76:1.00. **22**: IR (film) 3040, 3000, 2900, 2830, 2215, 1470, 1450, 1430, 1330, 1110, 1080, 1050, 1015, 755, 690 cm^{-1}; high-resolution mass spectrum calcd for $C_{29}H_{40}N_2O$ (M^+) 432.3140, found 432.3147.

(2*S*,3*S*,5*R*)-1-Methyl-5-nonyl-2-(phenylmethyl)-3-pyrrolidinol (1). To potassium (100 mg, 2.6 mmol) in Et_2O (2 mL) at 0 °C was added HMPA (0.5 mL) followed by a solution of nitriles **22** (43.3 mg, 0.1 mmol) and *t*-BuOH (100 mg, 1.35 mmol) in Et_2O (0.8 mL) and toluene (0.8 mL) (in the absence of toluene as cosolvent, reduction of the phenylmethyl substituent was also observed). The resultant mixture was stirred for 4 h at 25 °C and then diluted with hexane (4 mL). The organic phase was decanted and extracted with saturated aqueous NH_4Cl (6 × 3 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude product which exhibited olefinic resonances in its ^1H NMR spectrum. The crude material was diluted with absolute EtOH (5 mL) and transferred to a pressure bottle, and 10% Pd–C (3 mg) was added. The bottle was flushed with H_2, and the mixture was then stirred overnight under H_2 (40 psi). The reaction mixture was filtered through Celite with the aid of EtOAc/hexanes (for elution), and the organic phases were then concentrated *in vacuo* to furnish a red oil. Chromatography on silica gel (5% CH_3OH/CH_2Cl_2 for elution) afforded **1** (27 mg, 85%) as a waxy solid: $[\alpha]^{25}_D$ 30.0° (*c* 1.0 in $CHCl_3$), lit.[3] $[\alpha]^{25}_D$ +31.08° (*c* 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.10 (m, 5H, Ph), 3.86 (m, 1H, OC*H*), 2.90 (dd, *J* = 13.3 and 10.4 Hz, 1H, PhC*H*), 2.87 (dd, *J* = 13.3 and 4.3 Hz, 1H, PhC*H*), 2.40 (s, 3H, NCH_3), 2.35–2.10 (m, 3H, NC*H* and HC*H*), 1.80–1.15 (complex m, 17H, C*H* envelope), 0.85 (t, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 138.96, 129.36, 128.45, 126.24, 74.10, 70.19, 66.45, 39.29, 38.34, 34.03, 33.19, 31.87, 29.76, 29.56, 29.52, 29.26, 26.31, 22.64, 14.03; IR (film) 3360, 3015, 3000, 2920, 2900, 2830, 2760, 1480, 1455, 1130, 1025, 780, 695 cm^{-1}; high-resolution mass spectrum calcd for $C_{21}H_{34}NO$ ($M^+ - H$) 316.2641, found 316.2644.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **9a** and the diastereomeric nitriles **22** (8 pages). Ordering information is given on any current masthead page.